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(71) Applicant (for all designated States except US): **SEATTLE GENETICS, INC.** [US/US]; 21823 30th Drive SE, Bothell, WA 98021 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SEETER, Peter, D.** [US/US]; 9000 40th Avenue NE, Seattle, WA 98115 (US). **DORONINA, Svetlana** [RU/US]; 12001 Woodinville Drive, T-301, Bothell, WA 98011 (US). **TOKI, Brian, E.** [US/US]; 16720 6th Avenue West, C-204, Lynnwood, WA 98037 (US).

(74) Agents: **ANTLER, Adriane, M.** et al.; Jones Day LLP, 222 East 41st Street, New York, NY 10017 (US).

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(54) Title: DRUG CONJUGATES AND THEIR USE FOR TREATING CANCER, AN AUTOIMMUNE DISEASE OR AN INFECTIOUS DISEASE

(57) Abstract: Drug-Linker-Ligand Conjugates are disclosed in which a Drug is linked to a Ligand via a peptide-based Linker unit. In one embodiment, the Ligand is an Antibody. Drug-Linker compounds and Drug compounds are also disclosed. Methods for treating cancer, an autoimmune disease or an infectious disease using the compounds and compositions of the invention are also disclosed.

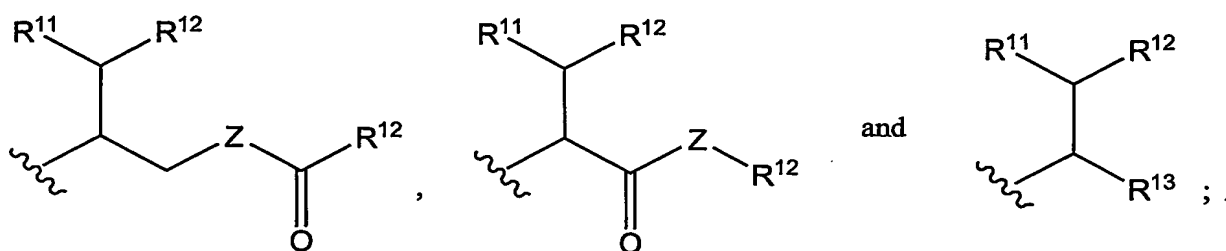


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AMENDED CLAIMS

received by the International Bureau on 16 June 2004 :

claims 1,5, 7 are amended, 93-119 are added, claims 2-4,6 and 8-92 are unchanged.

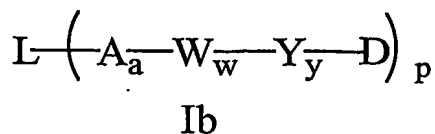
 R^6 is selected from -H and -C₁-C₈ alkyl; R^7 is selected from -H, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle);5 each R^8 is independently selected from -H, -OH, -C₁-C₈ alkyl, -C₃-C₈ carbocycle and -O-(C₁-C₈ alkyl); R^9 is selected from -H and -C₁-C₈ alkyl; R^{10} is selected from10 Z is -O-, -S-, -NH- or -N(R¹⁴)-;

R^{11} is selected from -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle); or R^{11} is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

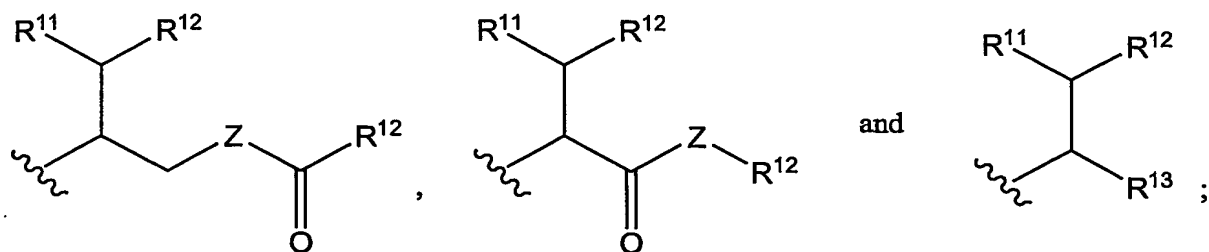
15 each R^{12} is independently selected from -aryl and -C₃-C₈ heterocycle; R^{13} is selected from -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle); and20 Each R^{14} is independently -H or -C₁-C₈ alkyl.

2. The compound of claim 1 wherein w is an integer ranging from 2 to 12.

3. A compound of the formula Ib:



or a pharmaceutically acceptable salt or solvate thereof



Z is -O-, -S-, -NH- or -N(R¹⁴)-;

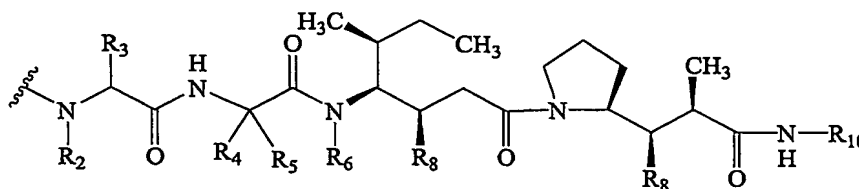
R¹¹ is selected from -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkyl), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), -C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle); or R¹¹ is an oxygen atom which forms a carbonyl unit (C=O) with the carbon atom to which it is attached and a hydrogen atom on this carbon atom is replaced by one of the bonds in the (C=O) double bond;

each R¹² is independently selected from -aryl and -C₃-C₈ heterocycle;

R¹³ is selected from -H, -OH, -NH₂, -NHR¹⁴, -N(R¹⁴)₂, -C₁-C₈ alkyl, -C₃-C₈ carbocycle, -O-(C₁-C₈ alkoxy), -aryl, -C₁-C₈ alkyl-aryl, -C₁-C₈ alkyl-(C₃-C₈ carbocycle), C₃-C₈ heterocycle and -C₁-C₈ alkyl-(C₃-C₈ heterocycle); and
each R¹⁴ is independently -H or -C₁-C₈ alkyl.

6. The compound of claim 5 wherein w is an integer ranging from 2 to 12.

7. A compound or a pharmaceutically acceptable salt or solvate of the compound of claim 1 where -D is a Drug unit having the structure



or a pharmaceutically acceptable salt or solvate thereof,

wherein, independently at each location:

R² is selected from -H and -methyl;

R³ is selected from -H, -methyl, and -isopropyl;

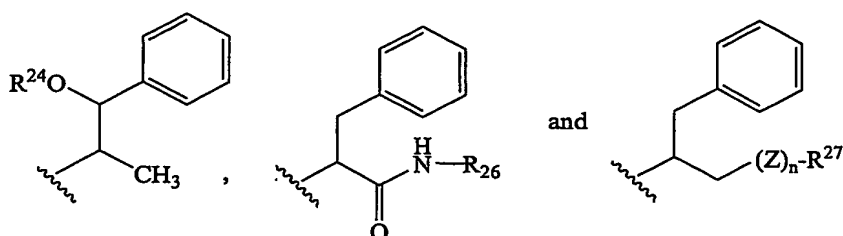
R⁴ is selected from -H and -methyl; R⁵ is selected from -isopropyl, -isobutyl, -sec-butyl, -methyl and -t-butyl or R⁴ and R⁵ join, have the formula - (CR^aR^b)_n- where R^a and R^b are independently selected from -H, -C₁-C₈ alkyl, and -C₃-C₈ carbocycle, and n is

selected from 2, 3, 4, 5 and 6, and form a ring with the carbon atom to which they are attached;

R^6 is selected from -H and -methyl;

each R^8 is independently selected from -OH, -methoxy and -ethoxy;

5 R^{10} is selected from



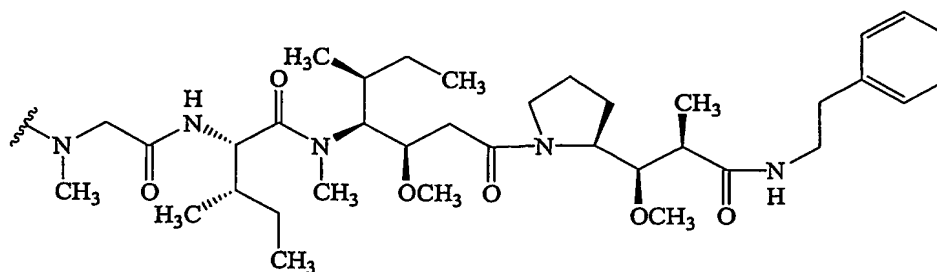
R^{24} is selected from H and $-C(O)R^{25}$; wherein R^{25} is selected from $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$ alkyl- (C_3-C_8) carbocycle, $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl- (C_3-C_8) heterocycle);

10 Z is -O-, -NH-, -OC(O)-, -NHC(O)-, $-NR^{28}C(O)-$; where R^{28} is selected from -H and $-C_1-C_8$ alkyl;

n is 0 or 1; and

R^{27} is selected from -H, $-N_3$, $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$ alkyl- (C_3-C_8) carbocycle, $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl- (C_3-C_8) heterocycle) when n is 0; and R^{27} is selected from -H, $-C_1-C_8$ alkyl, $-C_3-C_8$ carbocycle, -aryl, $-C_1-C_8$ alkyl-aryl, $-C_1-C_8$ alkyl- (C_3-C_8) carbocycle, $-C_3-C_8$ heterocycle and $-C_1-C_8$ alkyl- (C_3-C_8) heterocycle) when n is 1.

8. A compound or a pharmaceutically acceptable salt or solvate of the compound of claim 1 where -D is a Drug unit having the structure

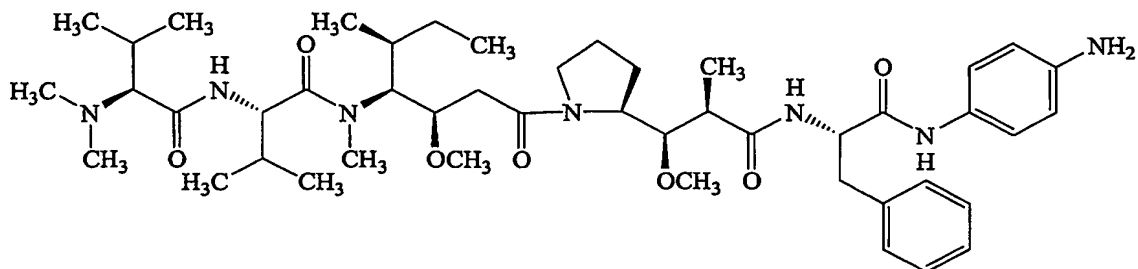


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9. A compound or a pharmaceutically acceptable salt or solvate of the compound of claim 1 where -D is a Drug unit having the structure

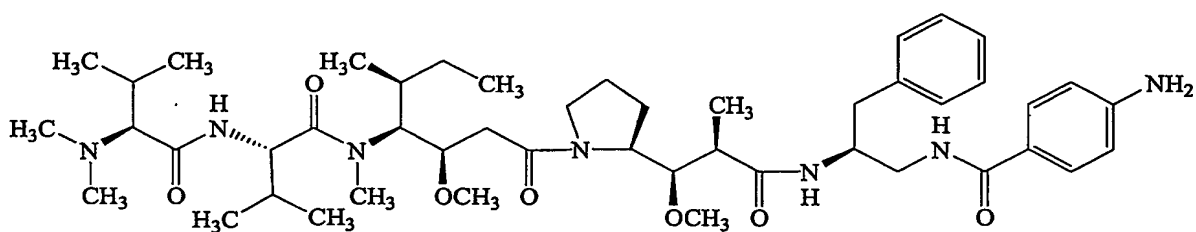
or a pharmaceutically acceptable salt or solvate thereof.

90. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof.

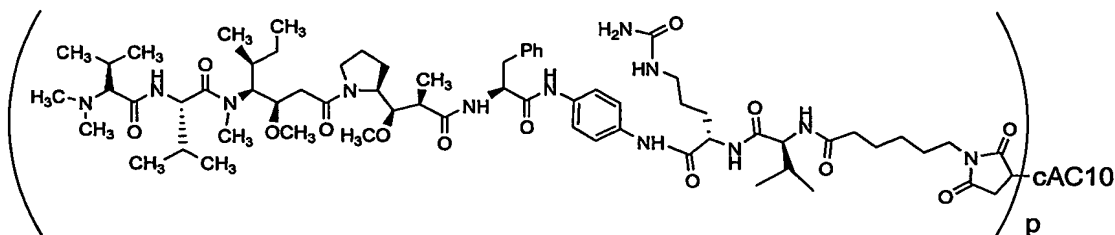
5 91. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof.

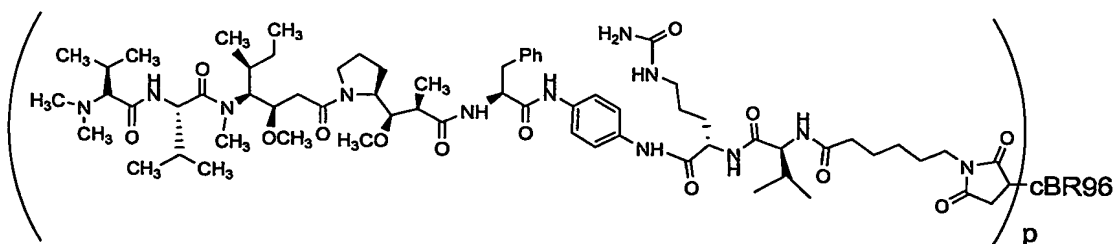
92. The compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 1, 3, 5, 32, 34, 35, 36, 37, 38, 43 or 44, in an isolated or a purified form.

10 93. A compound having the structure



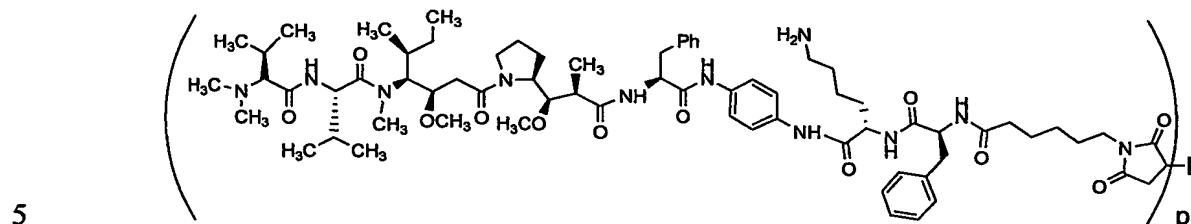
or a pharmaceutically acceptable salt or solvate thereof, where p ranges from about 7 to about 9.

94. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof, where p ranges from about 7 to about 9

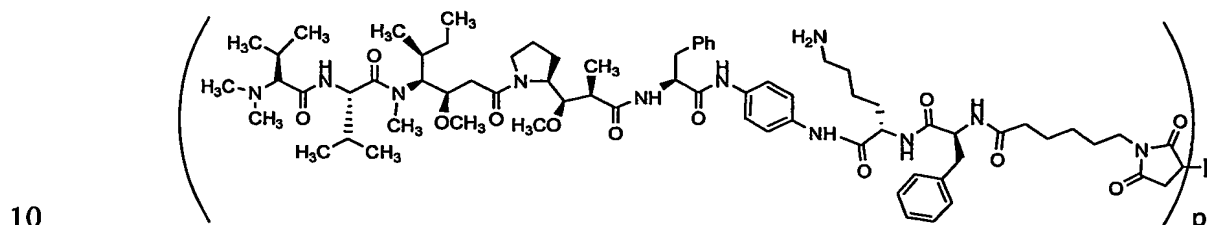
95. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof,
where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.

96. The compound of claim 95 wherein L is rituximab.

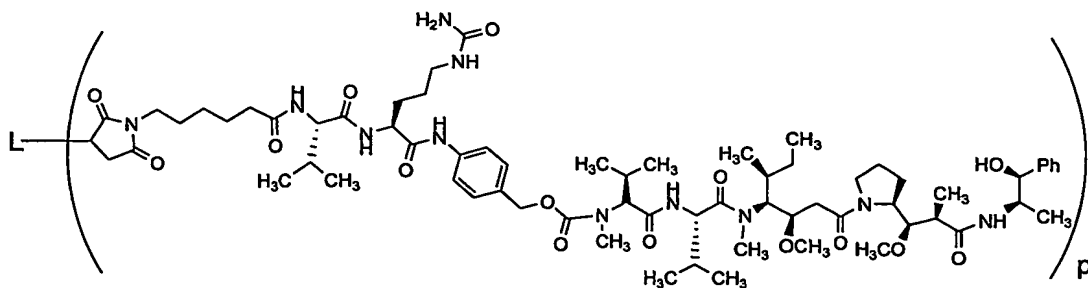
97. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof,
where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

98. The compound of claim 97 wherein L is S2C6.

99. A compound having the structure

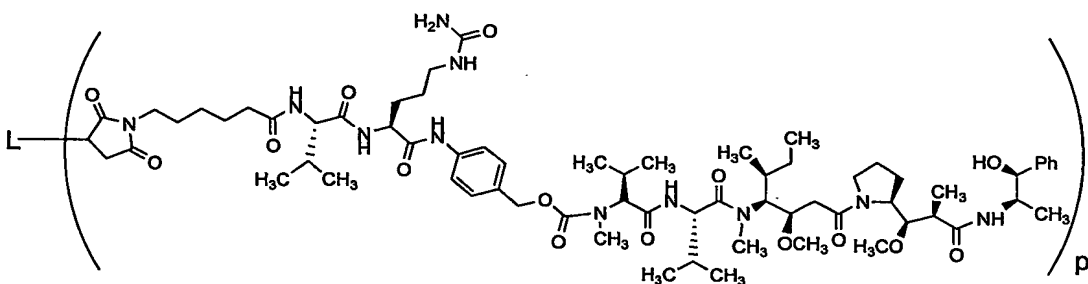


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.

100. The compound of claim 99 wherein L is rituximab.

5 101. A compound having the structure

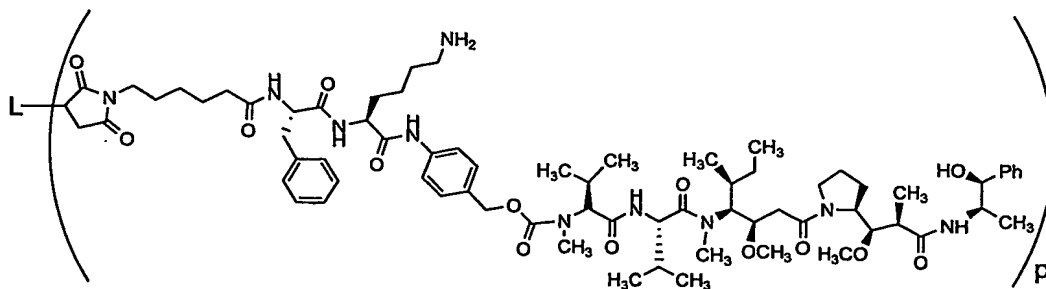


or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

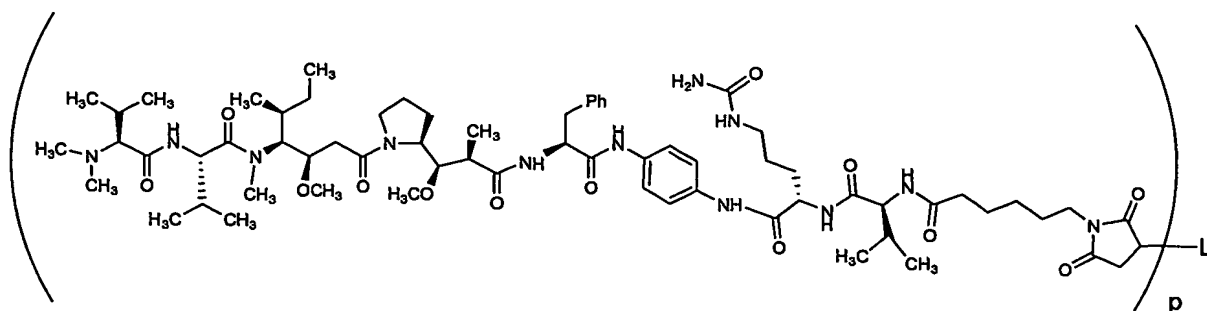
102. The compound of claim 101 wherein L is S2C6.

10 103. A compound having the structure



or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD20 antibody.



or a pharmaceutically acceptable salt or solvate thereof,

where p ranges from about 7 to about 9; and L is an anti-CD40 antibody.

110. The compound of claim 109 wherein L is S2C6.

111. A composition comprising an effective amount of a compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109 and a pharmaceutically acceptable carrier or vehicle.

112. A method for killing or inhibiting the multiplication of a tumor cell or cancer cell comprising administering to an animal in need thereof a therapeutically effective amount of a compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

113. A method for treating cancer, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or solvate of the compound of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

114. A method for treating an autoimmune disease, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or solvate of the compound of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

115. A method for treating an infectious disease, comprising administering to an animal in need thereof an effective amount of a compound or a pharmaceutically acceptable salt or solvate of the compound of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109.

116. The method of claim 113 further comprising administering to the animal an effective amount of an anticancer agent.

117. The method of claim 114 further comprising administering to the animal an effective amount of an immunosuppressant agent.

5 118. The method of claim 115 further comprising administering to the animal an effective amount of an anti-infectious agent.

119. The compound or a pharmaceutically acceptable salt or solvate thereof of any one of claims 77-91, 93-95, 97, 99, 101, 103, 105, 107 and 109, in an isolated or a purified form.